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Changes in Insulin Resistance After Initiation of Raltegravir or Protease Inhibitors With Tenofovir-Emtricitabine: AIDS Clinical Trials Group A5260s

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Background.   Antiretroviral therapy (ART) can alter glucose metabolism, but little data exist on the association of raltegravir (RAL) with insulin resistance.

Methods.   A5260s was a substudy of A5257, a prospective open-label randomized trial in which human immunodeficiency virus (HIV)-infected treatment-naive participants were randomized to tenofovir-emtricitabine (TDF/FTC) plus atazanavir-ritonavir (ATV/r), darunavir-ritonavir (DRV/r), or RAL over 96 weeks. Baseline and changes in insulin resistance as estimated by the homeostatic model assessment of insulin resistance (HOMA-IR) were assessed. Wilcoxon rank-sum tests were used to assess shifts in the distribution of fold increase from baseline between treatment arms, and Spearman correlation was used to assess associations between HOMA-IR and measures of inflammation and body composition.

Results.   Three hundred twenty-eight participants were randomized; 90% were male, baseline median age was 36, HIV ribonucleic acid copies were 4.55 $\log_{10}$ copies/mL, and CD4 cell count was 349/mm^3. Overall, HOMA-IR increased significantly after 4 weeks (1.9-fold change; 95% confidence interval, 1.73–2.05) then plateaued over the remainder of the study. Changes in HOMA-IR were not different between the arms ($P \geq .23$). Changes in HOMA-IR were associated with changes in body mass index at weeks 48 and 96 ($r = 0.12$–0.22; $P \leq .04$). There was a trend with increases in HOMA-IR and increases in visceral abdominal fat at week 96 ($r = 0.12$; $P = .06$). At 48 and 96 weeks, HOMA-IR correlated with interleukin-6, high-sensitivity C-reactive protein, and soluble CD163 ($r = 0.16$–0.27; $P \leq .003$).

Conclusions.   Insulin resistance increased rapidly and then plateaued in treatment-naive participants initiating ART with TDF/FTC, and no differences were found with RAL when compared with ATV/r or DRV/r.

Keywords.   inflammatory markers; insulin resistance; raltegravir.

Disorders of glucose metabolism are common amongst human immunodeficiency virus (HIV)-infected adults [1] with higher prevalence noted in HIV-infected individuals compared with healthy controls [2]. The mechanisms are likely multifactorial including direct effects of HIV [3], antiretroviral therapy (ART) [4, 5], inflammation [6], and traditional risk factors [7]. Diabetes mellitus in this population can lead not only to cardiovascular diseases (CVDs) [8], but it can also compound other end organ dysfunctions associated with HIV such as renal [9] and neurologic complications [10]. Exposure to nucleoside reverse-transcriptase inhibitors (NRTIs) (particularly the thymidine analogs) [4, 5, 11] and protease inhibitors (PIs) [3, 12, 13] has been associated with an increase risk in diabetes and insulin resistance. It has been hypothesized that changes in adipose tissue (both central fat accumulation and peripheral lipoatrophy) seen with NRTIs and PIs could mediate and contribute to insulin resistance via lipotoxicity and mitochondrial derangement [14, 15].

Little data exist on the effect of integrase inhibitors and specifically raltegravir (RAL) on glucose metabolism. A small, single-arm, open-label study of 30 participants on RAL combined with tenofovir/emtricitabine (TDF/FTC) reported no increase in insulin resistance over 104 weeks [16]. Another study comparing patients on lopinavir/ritonavir plus RAL to lopinavir/ritonavir plus NRTIs suggested no difference in insulin resistance between the arms over 48 weeks [17].

The objective of the current study was to describe the changes in insulin resistance over 96 weeks after initiating TDF/FTC plus either atazanavir/ritonavir (ATV/r), darunavir/ritonavir (DRV/r), or RAL in HIV-infected individuals naive to treatment. We explored the time course and associations between regional fat changes, body mass index (BMI), and insulin

resistance because it is well known that adipose tissue plays a role in glucose metabolism, and fat changes in HIV have been associated with insulin resistance [14]. We also further examined the associations between markers of inflammation and immune activation and insulin resistance over time.

METHODS

A5260s was a substudy of AIDS Clinical Trials Group (ACTG) A5257 in which HIV-infected ART-naive participants ≥18 years of age with HIV-1 ribonucleic acid (RNA) ≥1000 copies/mL were randomized in an open-label fashion to receive TDF/FTC (300 mg of TDF plus 200 mg of FTC) plus either ATV/r (300 mg of ATV plus 100 mg of ritonavir once daily), DRV/r (800 mg DRV plus 100 mg ritonavir once daily), or RAL (400 mg twice daily). A5257 participants without known CVD or diabetes mellitus, uncontrolled thyroid disease, or use of lipid-lowering medications were eligible to enroll in A5260s. Randomization was stratified by screening HIV-1 RNA level (>100 000 or ≤100 000 copies/mL) and Framingham 10-year CVD risk score (<6% risk or ≥6% risk). A5260s primary objectives were to compare atherosclerosis progression and endothelial function between the randomized regimens [18], and secondary objectives included assessing changes in immune activation markers and body composition [19–21]. A secondary objective was to examine the effects of A5260s regimens on markers of insulin resistance. The parent study and substudy (clinicalTrials.gov NCT00811954 and NCT00851799) were approved by the Institutional Review Boards at participating institutions, and participants provided written informed consent.

Insulin Resistance Measure
Fasting glucose and insulin were measured at baseline and weeks 4, 24, 48, and 96. Insulin resistance was estimated by homeostasis model assessment-insulin resistance (HOMA-IR) index [22]. The HOMA-IR was obtained using the following calculation: $\log_{10}$ (HOMA-IR) = $\log_{10}$ (glucose (mg/dL) × $\log_{10}$ (insulin (IU)/405)). Insulin resistance was defined as HOMA-IR >2.5.

Body Composition Measures
The BMI was measured at the same visits as insulin and glucose. Substudy body scan evaluations occurred at baseline and week 96. Body composition was measured as previously detailed [20]. Single-slice computed tomography (CT) scan at the L4-L5 level was used to quantify visceral adipose tissue (VAT), subcutaneous adipose tissue, and total adipose tissue. Scans were standardized and centrally read by blinded personnel at the Body Composition Analysis Center at Tufts University (Boston, MA) (DXA) and LA Biomed (Torrance, CA) (CT).

Laboratory Assessment
Blood samples (fasting for ≥8 hours) were collected. Serum insulin was measured by commercial testing at Quest Diagnostics by radioimmunoassay. Plasma biomarkers were measured at the University of Vermont Laboratory for Clinical Biochemistry Research Laboratory (Burlington, VT) on batched plasma samples that were stored at −70°C degrees and not previously thawed, and these included high-sensitivity C-reactive protein (hsCRP) by nephelometry, D-dimer with immunoturbidimetric methods, and soluble (s)CD14, sCD163, interleukin (IL)-6, by enzyme-linked immunosorbent assay.

Statistical Analysis
The primary objective of this analysis was to determine the extent to which insulin resistance as measured by HOMA-IR changed over time after initiating the randomized treatments and to compare these changes between arms. The HOMA-IR was transformed to the $\log_{10}$ scale for all analyses. Changes over time in glucose are shown as median (interquartile range [IQR]) absolute change from baseline for each study week; changes over time in HOMA-IR are shown as median (IQR) fold change from baseline; HOMA-IR results were back-transformed for this calculation. Wilcoxon rank-sum tests were used to assess shifts in the distribution of change from baseline between treatment arms; *P* values were adjusted using Benjamini-Hochberg methods to control false-discovery rate (FDR) due to a multitude of biomarker assessments (some previously published [19]). Spearman rank correlations quantified associations between HOMA-IR and body composition measures and with inflammatory markers; partial correlations were used for adjusted comparisons. All pairwise-treatment group comparisons were assessed with an FDR of 2.5%, and all other comparisons were at a 5% alpha level. Analyses were conducted as intent-to-treat (ITT); an as-treated secondary analysis showed similar results to the ITT analysis (data not shown).

RESULTS

Baseline Characteristics and Disposition
As seen in Table 1, a total of 328 participants entered A5260s (109 randomized to ATV, 106 to RAL, and 113 to DRV). Overall, median age was 36 years and 90% were male. The median CD4 count was 349 cells/μL, HIV RNA copies 4.55 $\log_{10}$ copies/mL, BMI was 25 kg/m², and VAT 72.9 cm². Of the 328 participants enrolled, 324 had HOMA-IR at baseline (107 in ATV arm, 105 in RAL, and 112 in DRV). Median baseline HOMA-IR was 0.59 and 10% of participants had HOMA-IR >2.5.

Changes in Homeostasis Model Assessment-Insulin Resistance and Glucose Levels
The HOMA-IR increased rapidly from baseline to week 4 in all 3 treatment arms with a median (Q1, Q3) fold change of 2.05 (1.35, 3.45) on ATV/r, 1.95 (1.08, 2.78) on RAL, and 1.84 (1.14, 2.74) on DRV/r, and not different between the 2 PI arms (*P* = .23) or between RAL and each of the PI/r arms (*P* ≥ .32). Overall, 22% of participants had HOMA-IR >2.5 at week 4. This rapid increase in HOMA-IR plateaued for the remainder of the study in all treatment arms as seen in Table 2 and Figure 1

Table 1. Baseline Characteristics[a]

Characteristics	ATV/r (n = 109)	RAL (n = 106)	DRV/r (n = 113)
Age (y)	37 (31–45)	36 (27–44)	35 (27–46)
Sex			
M	99 (91%)	94 (89%)	101 (89%)
F	10 (9%)	12 (11%)	12 (11%)
Race/ethnicity			
White	53 (49%)	43 (41%)	48 (42%)
Blacks	34 (31%)	34 (32%)	37 (33%)
Hispanics	20 (18%)	20 (19%)	25 (22%)
Current smoking	44 (40%)	39 (37%)	41 (36%)
Family history of diabetes	33 (30%)	22 (21%)	26 (23%)
CD4$^+$ cell count (/mm^3)	350 (211–461)	343 (185–445)	355 (207–461)
HIV-1 RNA (log$_{10}$ copies/mL)	4.62 (4.05–5.10)	4.52 (4.13–5.08)	4.52 (3.95–4.95)
HIV-1 RNA			
<100 000 copies/mL	78 (71%)	74 (69%)	86 (76%)
≥100 000 copies/mL	31 (29%)	32 (31%)	27 (24%)
Weight (kg)	80 (69–88)	77 (66–89)	77 (67–83)
Body mass index (kg/m^2)	26 (23–29)	24 (22–28)	24 (22–27)
Visceral adipose tissue (cm^2)	78.2 (42.6–111.3)	75.3 (41.6–110.1)	59.8 (32.8–99.2)
Glucose (mg/dL)	83 (77–91)	82 (76–91)	82 (78–88)
Insulin (μIU/dL)	3 (2–7)	3 (2–7)	2 (2–6)
HOMA-IR (log$_{10}$)	−0.21 (−0.40 to 0.18)	−0.14 (−0.39 to 0.14)	−0.33 (−0.41 to 0.12)
HOMA-IR >2.5	10 (9.4%)	9 (8.6%)	12 (10.7%)

Abbreviations: ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; HIV, human immunodeficiency virus; HOMA-IR, homeostatic model assessment of insulin resistance; RAL, raltegravir; RNA, ribonucleic acid.

[a] Median values (interquartile range) or n (%).

with a median fold change of 1.75–2.06 for all study weeks and no differences between arms ($P \geq .18$). The number of participants with abnormal HOMA-IR also did not increase for the remainder of the study (24%–25% of participants had HOMA-IR >2.5 through week 96). Glucose also increased by week 4 with an absolute change of 3 (−2, 8) in the ATV/r and RAL arms and 2 (−3, 7) in the DRV/r arm ($P \geq .5$ between arms).

Table 2. Median (IQR) Change From Baseline in Glucose and HOMA-IR by Treatment Arm Over Time[a]

Glucose/HOMA-IR	ATV/r	RAL	DRV/r
Glucose (mg/dL)			
Week 4	3 (−2 to 8)	3 (−2 to 8)	2 (−3 to 7)
Week 24	4 (−1 to 8)	4 (0–10)	4 (−3 to 8)
Week 48	4 (−2 to 14)	4 (−2 to 10)	2 (−5 to 7)
Week 96	3 (−2 to 10)	6 (2–13)	2 (−2 to 8)
HOMA-IR			
Week 4	2.05 (1.35–3.45)	1.95 (1.08–2.78)	1.84 (1.14–2.74)
Week 24	2.06 (1.30–3.39)	1.84 (1.13–2.69)	1.83 (1.05–2.71)
Week 48	1.96 (1.12–3.98)	1.75 (1.13–3.11)	1.83 (1.00–3.13)
Week 96	2.02 (1.10–3.06)	2.00 (1.08–3.32)	1.88 (1.01–2.92)

Abbreviations: ATV/r, atazanavir-ritonavir; DRV/r, darunavir/ritonavir; HOMA-IR, homeostatic model assessment of insulin resistance; IQR, interquartile range; RAL, raltegravir.

[a] Glucose changes presented as median absolute changes. HOMA-IR changes presented as fold changes.

Linear regression analyses assessed association of baseline factors including gender, age, viral load, CD4 count, and inflammation markers, with changes in HOMA-IR from baseline to week 4 as well as changes from baseline to week 96. The only baseline factor associated with change in HOMA-IR at week 4 was male gender ($P = .005$), whereas baseline male gender, higher baseline sCD14, and higher baseline IL-6 were associated with larger HOMA-IR change at week 96 ($P \leq .04$).

Changes in Homeostasis Model Assessment-Insulin Resistance in Relation to Fat and Body Mass Index Changes

Although DXA scan was not performed at week 4, changes in HOMA-IR seemed to occur much earlier than changes in fat depots (see Figure 2). We have previously shown that all 3 regimens were associated with similar increases in VAT by week 96 with a mean change of 25.8%. As shown in Figure 2, there was a trend for a correlation between increases in HOMA-IR and increases in VAT at week 96 ($r = 0.12$, $P = .06$). Changes in HOMA-IR correlated with changes in total fat at week 96 ($r = 0.17$, $P = .005$). Changes in HOMA-IR modestly correlated with changes in BMI only at week 48 ($r = 0.12$, $P = .04$) and week 96 ($r = 0.22$, $P = .005$) (see Figure 3).

Association Between Inflammatory Markers and Homeostasis Model Assessment-Insulin Resistance at Baseline and Weeks 48 and 96

As shown in Table 3, higher values of HOMA-IR at baseline were associated with D-dimer at baseline ($r = 0.14$, $P = .01$)
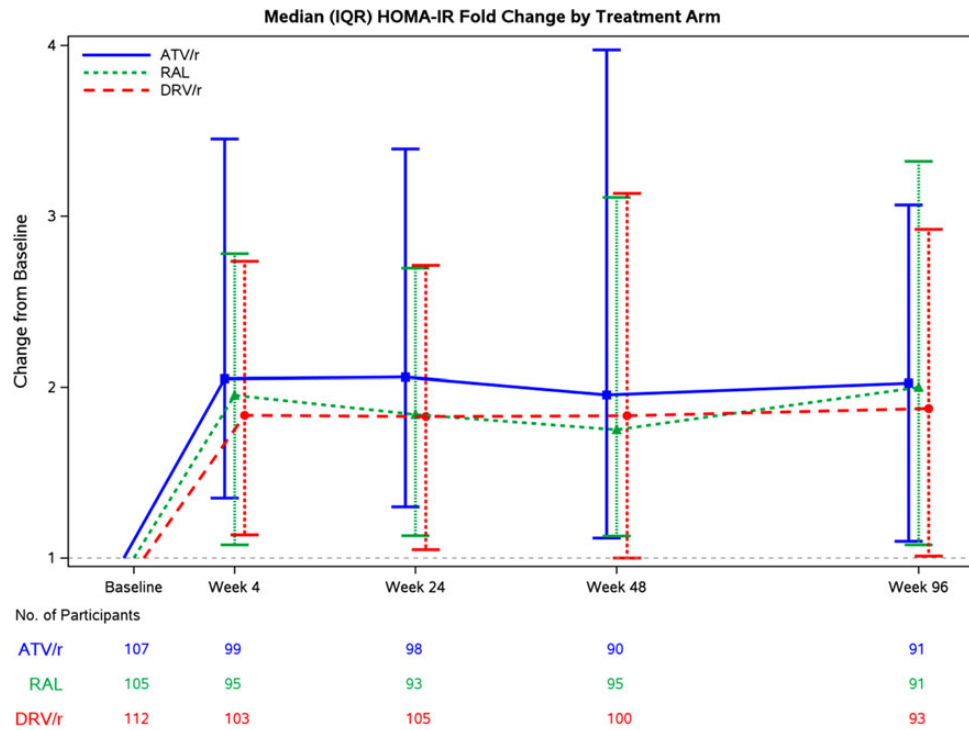
Figure 1. Changes in homeostatic model assessment of insulin resistance (HOMA-IR) over time by treatment arm. Median fold change in HOMA-IR from baseline by treatment arm. Error bars represent interquartile range (IQR). Abbreviations: ATV/r, atazanavir-ritonavir; DRV/r, darunavir/ritonavir; RAL, raltegravir.
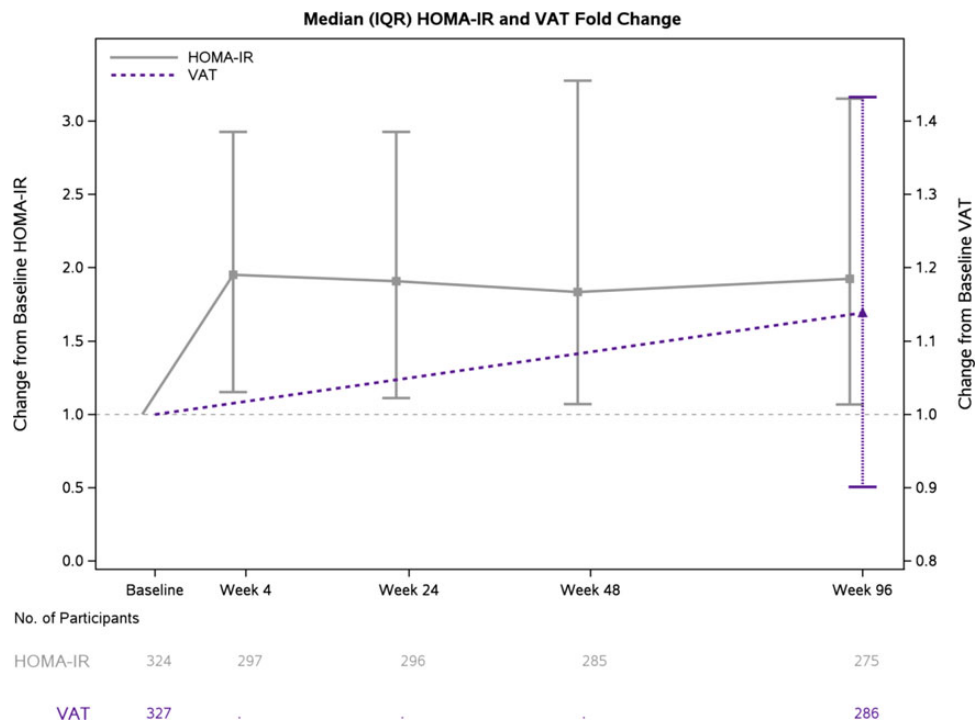
Figure 2. Association between change in homeostatic model assessment of insulin resistance (HOMA-IR) and change in fat depot. Median fold change from baseline between HOMA-IR and visceral fat. Error bars represent interquartile range (IQR). Abbreviation: VAT, visceral adipose tissue.
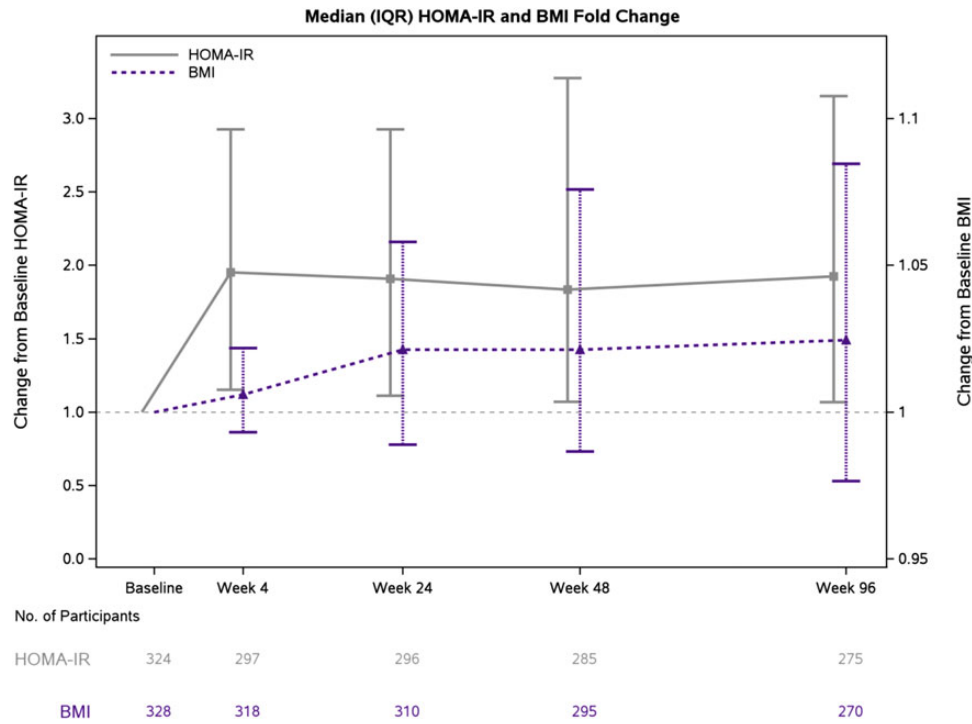
Figure 3. Changes in homeostatic model assessment associated with changes in body mass index (BMI). Median fold change from baseline between homeostatic model assessment of insulin resistance (HOMA-IR) and BMI. Error bars represent interquartile range (IQR).

but not with other markers of systemic inflammation or monocyte activation ($P \geq .06$). In contrast, at weeks 48 and 96, HOMA-IR was associated with weeks 48 and 96 hsCRP ($r = 0.24$–0.27, $P < .001$), IL-6 ($r = 0.18$–0.27, $P \leq .003$), and with sCD163 ($r = 0.16$–0.19, $P \leq .008$). After adjusting for parameters known to affect insulin resistance, such as age, sex, BMI, and family history of diabetes, sCD163 still remained

Table 3. Baseline Factors Association With Baseline HOMA-IR (Log$_{10}$)

Baseline Characteristics	Spearman r	P Value
Demographics and clinical parameter		
Age	0.12	.04
BMI	0.33	<.001
HIV-specific factors		
Baseline CD4	−0.07	.22
HIV RNA (log$_{10}$ copies/mL)	−0.01	.90
Markers of Inflammation and Immune Activation		
Interleukin-6	0.10	.06
hsCRP	0.09	.13
D-Dimer	0.14	.01
sCD163	0.04	.46
sCD14	−0.06	.33
sIL-2	−0.04	.46

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus; HOMA-IR, homeostatic model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; RNA, ribonucleic acid; s, soluble.

associated with HOMA-IR after 96 weeks of ART ($r = 0.14$, $P = .026$).

DISCUSSION

In this study, we show for the first time a significant and similar increase in insulin resistance after 4 weeks of treatment with the ritonavir-boosted PIs ATV and DRV compared with those treated with the integrase inhibitor RAL. In addition, HOMA-IR increases were most pronounced in the first 4 weeks and after a longer duration of ART, correlated with several markers of inflammation.

There is evidence that different PIs may differentially affect glucose metabolism. Indinavir [23] and, in some studies [24] but not all [25], LPV/r have been associated with insulin resistance both in HIV-infected patients and in healthy subjects [23, 24]. On the other hand, ATV/r and DRV/r seem to have minimal impact on insulin sensitivity both in HIV-infected and HIV-negative subjects [24, 26–29]. In a smaller study, where HIV-infected, treatment-naive patients were randomized to either DRV/r (n = 28) or ATV/r (n = 27) with TDF/FTC, no significant changes were seen in HOMA-IR from baseline at week 12 or 48 [26]. In the study presented here, participants randomized to either DRV/r or ATV/r regimens developed a rapid and similar increase in HOMA-IR with a 2-fold increase by 4 weeks of treatment. The baseline characteristics were similar between the 2 studies, and the differences could be due to the smaller

number of participants. In addition, HOMA-IR slightly decreased in their study, but these changes are difficult to compare because changes in HOMA-IR are reported as absolute change, whereas we report fold change.

The RAL-containing regimen similarly impaired insulin sensitivity as the boosted PI arms both in timing and in magnitude. One possible hypothesis is that changes in HOMA-IR were the result of TDF-FTC and not RAL or PIs. However, we have shown that changes in insulin resistance were similar when ART-naive participants were randomized to TDF/FTC or abacavir/lamivudine-based regimen [30].

We had anticipated that increases in fat depots, specifically VAT, which is most closely associated with insulin resistance, would be correlated with increases in HOMA-IR. However, changes in insulin resistance occurred early, after only 4 weeks of treatment, and was associated with changes in BMI at 48 and 96 weeks. We hypothesize that (1) insulin resistance is likely multifactorial and early changes are independent of fat changes and (2) insulin resistance may lead to visceral fat by inhibiting lipolysis and early changes may be due to an alternate mechanism either by direct inhibition of glucose transport [31] as has been documented with PIs.

Another potential pathway for disorders of glucose metabolism in HIV is via generalized inflammation [6]. Systemic inflammation as well as markers of immune activation sCD163 and sCD14 have been linked to insulin resistance in the general population [32, 33]. We have previously shown that tumor necrosis factor (TNF)α activation is linked to incident diabetes after ART initiation in HIV-infected adults [6]; however, markers of monocyte activation were not measured in that study. The HOMA-IR was not correlated with sCD14 in a study of HIV-infected participants on ART [34]. In this trial, we found that inflammatory markers IL-6 and hsCRP as well as marker of monocyte activation sCD163 were associated with increase in HOMA-IR after a longer duration of ART, but not before ART. This is clinically relevant because these markers have also been associated with CVD risk [35]. A novel finding is our observed relationship between insulin resistance and the marker of monocyte activation sCD163 in HIV-infected adults. Soluble CD163 has been associated with HOMA-IR in healthy adults [33]; in HIV, 1 study describes an association between adiposity and sCD163, which was slightly decreased when adjusting for insulin resistance [36]. It is interesting to note that there was no correlation at baseline; however, even after adjusting for variables known to affect insulin resistance, such as age, gender, BMI, and family history of diabetes, sCD163 remained associated with HOMA-IR after 96 weeks of ART. Unlike what we have found in our previous study in HIV-infected adults, sTNFα receptors were not significantly correlated with insulin resistance [6]. A potential explanation is that TNFα has a short half-life unlike CD163-expressing macrophages. Microbial translocation may also play a role in the association seen between sCD163 and insulin resistance. Markers of microbial translocation have been associated with insulin resistance [37] and are known to stimulate the release of sCD163 [38].

Although the primary strength of our study is the randomized study design with 2 different boosted PI regimens and RAL arms, there are several limitations. We recognize that the majority of participants are not insulin resistant (with HOMA-IR <2.5); however, it is well known that there is variability in the threshold to define insulin resistance as HOMA-IR based on age, gender and cardiometabolic risks [39]. Our cohort is relatively young and predominantly male, and diabetics were excluded; therefore, these results may not be applicable to women, older patients, in which the rates of insulin resistance may be greater, or to those with diabetes. The clinical significance of these changes in HOMA-IR is unclear; however, the rapid and persistent 2-fold increase raises concerns that these young participants may be at increased risk of developing abnormal glucose tolerance in the future. In addition, we used HOMA-IR as a measure of insulin resistance as opposed to the euglycemic-hyperinsulinemic clamp technique. However, HOMA-IR has been shown to correlate with the euglycemic-hyperinsulinemic clamp technique [40]. We did not collect information on dietary intake, which may affect insulin resistance. Although fat changes were unlikely to occur very early, CT scans were not obtained at week 4. There are no data describing such acute VAT changes in HIV-infected adults on ART. Dube et al [41] measured trunk fat at 16 weeks in HIV-infected adults on ART and described a small increase (5%–7%).

CONCLUSIONS

In conclusion, we found that insulin resistance increased similarly in RAL and boosted PI regimens, before an increase in BMI and before the expected development of fat changes. Persistent increase in insulin resistance after 48 and 96 weeks of ART may be associated with systemic inflammation and immune activation. The mechanisms that underlie the prompt impairment of insulin sensitivity after starting ART require further investigation.

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